DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To:	BLA STN 125487/0, Coagulation Factor VIII (Recombinant), Fc fusion protein (rFIVIIIFc)
From:	Jie He, M.S., CSO, OCBQ/DMPQ/MRB II, HFM-676
Through:	Marion Michaelis, Branch Chief, OCBQ/DMPQ/MRB II, HFM-676
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	Ellen Huang, Consult, CSO, OCBQ/DMPQ/MRB II, HFM-676
Subject:	Addendum Review of the BLA submitted by Biogen Idec Inc., Lic. #1697, to provide for marketing of Coagulation Factor VIII (Recombinant), Fc fusion protein (rFIVIIIFc).
Due Date:	June 7, 2014

REVIEW RECOMMENDATIONS

I recommend approval base on the review of the firm's response and additional information submitted.

Additionally, I recommend the following items should be evaluated on the next inspection:

- ------b(4)/b(7)(e)---------- ----------

- ----- b(4)/b(7)(e)---------- ----------

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- ---- b(4)/b(7)(e)---- ----------

- ---- b(4)/b(7)(e)---------- ----------.

REVIEW SUMMARY

Biogen Idec Inc. (Biogen) submitted an original application under STN 125487/0 for the licensure of Antihemophilic Factor (Recombinant), Fc Fusion Protein (rFVIIIFc), Recombinant Factor VIII Fusion Protein (rFVIIIFc) for the treatment of hemophilia A. The BLA was received by CBER on March 8, 2013. rFVIIIFc drug substance is produced at the –b(4)--------- scale at Biogen Idec facilities located in Cambridge, Massachusetts. The rFVIIIFc drug product (DP) is manufactured for Biogen Idec –b(4)----------. The Sterile Water for Injection (SWFI) pre-filled syringes are manufactured under contract by –b(4)----------
Please refer to my primary discipline review memo for a review of the BLA STN 125487/0.

This review memo is an addendum that covers the Amendments STN 125487/0/1, STN 125487/0/21, STN 125487/0/23, STN 125487/0/24, STN 125487/0/25, STN 125487/0/26, STN 125487/0/27, STN 125487/0/28, STN 125487/0/30, STN 125487/0/31, STN125487/0/36, STN125487/0/37,STN125487/0/38 and STN125487/0/40.

FDA sent a letter to Biogen Idec on December 4, 2013 to indicate that Amendment STN 125487/0/27 received on November 15, 2013 was considered a major amendment. DMPQ IR questions were sent to the firm on April 26, May 30, 2013, September 11, 2013, November 1, 2013, November 21, 2013 and March 20, 2014. Additionally, telecons were held with the firm on May 29, 2013, September 11, October 8, October 25, October 21, November 22, and March 28, 2014.

As this is a recombinant product, this review was conducted under FDA's Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-derived Product or a Monoclonal Antibody Product for In Vivo Use. Under this guidance, limited information is required to be submitted regarding facility and equipment. As such, my review is based on this guidance document.

I. NARRATIVE REVIEW

Items Reviewed

Amendments STN 125487/0/1, STN 125487/0/21, STN 125487/0/23, STN 125487/0/24, STN 125487/0/25, STN 125487/0/26, STN 125487/0/27, STN 125487/0/28, STN 125487/0/30, STN 125487/0/31, STN125487/0/36, STN125487/0/37, STN125487/0/38, and STN125487/0/40.

Review of Amendment STN 125487/0/1 (April 10, 2013)

FDA communicated to Biogen on April 5, 2013 that the original BLA did not contain FEI numbers for two of the –b(4)----- facilities in b(4) used for ---b(4)----------, and CBER received responses from the sponsor in amendment STN 125487/0/1 on April 10, 2013 providing FEI numbers for the two facilities.

Reviewer's Comments: The firm provided the requested information. The response is acceptable.

Review of Amendment STN 125487/0/21 (October 16, 2013)

A telecon was requested by Biogen to discuss mid-cycle IR Questions 24, 25 and 29. This amendment contains briefing package for the telecon which was held on October 23, 2013. Question 29 was a DMPQ item. Biogen provided description of the DS manufacturing facility including specific manufacturing activities and their locations inside the building. It described the utilization of –b(4)----------, and purification suites in the Purification b(4) area. Review of this facility issue is also discussed in the primary review memo on page 17 and in Amendment 24 below.

Review of Amendment STN 125487/0/23 (October. 31, 2013)

A telecon was held with Biogen on Oct. 8, 2013 to discuss lyophilization issues including equipment qualification, empty chamber and technical run protocols. FDA discussed the lyophilization validation methodology and advised Biogen to submit validation protocol for review before conducting the study. This amendment contains the draft protocol for the empty chamber study for qualification of the lyophilizer (b(4)) used to manufacture rFVIIIFc drug product at –b(4)-- site. It described ----------b(4)---------- ---------- The protocol described –b(4)--------- locations and acceptance criteria with regards to the maximum difference between an individual –b(4)---------- and the –b(4)----------for each of the –b(4)---------- during the qualification cycle when using –b(4)--------. The acceptance criteria are:

1. ---b(4)---------- ----------.
2. -----b(4)---------- ----------.

These acceptance criteria will be utilized for the three qualification cycles using –b(4)------ Each qualification cycle will utilize -----b(4)----------

Reviewer's comment: We stated that –b(4)------ is required by the Agency, Biogen can chose to conduct both studies. The sampling plan is acceptable, but that we had concerns with

respect to the proposed acceptance limit of –b(4)---------- is the current normal industry practice. We stated that we will wait and see the actual study report when completed, then discuss this issue again. We conveyed to Biogen that the protocol is acceptable.

Review of Amendment STN 125487/0/24 (Oct. 31, 2013)

Biogen requested a telecon held on October 23, 2013 seeking clarification on mid-cycle IR question 24, 25 and 29. Question 29 is DMPQ item regarding licensing of manufacturing areas. This Amendment contains the telecon minutes and additional information for facility, equipment and environmental monitoring (EM) data for purification suites for the period when conformance lots were manufactured.

Mid-cycle IR Question 29

Regarding licensing of manufacturing areas:
Please be advised that only the manufacturing areas through which conformance batch/lot manufacture has been successfully performed will be licensed

Biogens response:
Biogen provided following items related to licensing of Biogen Idec's Cambridge facility manufacturing areas for manufacture of rFVIIIFc drug substance:

- Specific areas and equipment used in the rFVIIIFc process validation campaign;
- Clarification of areas within the Cambridge facility that are considered closed and additional description of closed system;
- Clarification on equipment movement and traceability;
- Environmental monitoring summary for the -b(4)- equivalent suites within the Purification –b(4)- area, and
- In-process –b(4)---------- and drug substance release testing results from –b(4)----------

----b(4)---------- ----------

----b(4)-- ----------

---------- -----b(4)---- ----------

Due to the equivalency of the purification suites and portable nature of process equipment, Biogen proposes any of the -b(4)-- suites can be used for rFVIIIFc commercial manufacturing purification.

Biogen has change over procedures to prevent cross contamination that include equipment cleaning, elastomer change out, color coding in conjunction with room color coding, quality controlled documentation, and HVAC rebalancing.

Biogen provided EM data for suites –b(4)---------- covering first two quarters of 2013, and in-process –b(4)---------- and drug substance release testing results from b(4) batches made in –b(4)----------

[b(4)]

1 page determined to be not releasable: b(4)

[**b(4)**]

Reviewer's Comments:

Biogen requested licensing of –b(4)---------- purification suites (-b(4)----------) in Purification b(4) area. –b(4)---------- were used for process validation batches, so –b(4)- can be licensed. Regarding the –b(4)-- purification suites, the process validation lots were manufactured in –b(4)--, and –b(4)-- DS lots were manufactured in –b(4)--- post the validation lots. No conformance batches were manufactured in –b(4)---. On 10/23/2013, FDA and Biogen held a telecon to discuss the Purification b(4) area, FDA requested EM data for the purification suites during manufacturing of the conformance lots. Considering that the –b(4)- Class –b(4)- suites have -----b(4)--- ----------, and all have the same EM program, we agreed to consider licensing all –b(4)--- suites if the EM data shows that all –b(4)--suites are well controlled and monitored even though –b(4)------ has not been used for manufacturing any DS lot. The EM data submitted in this Amendment showed the –b(4)- suites were well controlled and no noticeable difference in excursion rate. The DS batches (nonconformance batches) manufactured in ----b(4)----- ----------. Based on the information, the –b(4)--purification suites can be considered as identical in physical layout, environmental control and functioning, so I recommend all –b(4)---- suites for DS manufacturing to be approved.

Review of Amendment STN 125487/0/25 (Nov. 6, 2013)

Response to DMPQ Mid cycle IR Q1 to Q10

Question 1

Regarding ----(b)(4)-------:

a. Please provide the -------(b)(4)------- validation studies for the –b(4)--- of vials used for the drug product, and for the syringe barrel and plunger used for the diluent.

Biogen's response

<u>rFVIII Drug Product-Vial</u>

The vial washing machine is utilized for washing of vials to be used in the filling process of -b(4)-. It is re-qualified –b(4)---. The re-qualification includes----b(4)---------- in the vials after the –b(4)----------. The results of the

recent re-qualification were provided. Sterilization and -------*(b)(4)*----- of empty vials occur in a ---b(4)---------- is re-qualified –b(4)--------- including the validation of specific cycles. All process cycles are based on the parameters successfully validated in the qualification programs. The -------*(b)(4)*----- process of the vials is validated to guarantee –b(4)---------- are summarized in the requalification summary report (-b(4)--, DOC. 5018732), and showed ---b(4)----------

[b(4)]

Due to the similarity of the vials from the –b(4)---------- (see response to Question 3), the firm did not perform a vial supplier specific validation.

rFVIIIFc Diluent-Syringe Barrel and Plunger

The syringe washing machine –b(4)---------- is utilized for washing of syringes to be used in the filling process of –b(4)--. It is re-qualified –b(4)--------. The results of the recent re-qualification are provided. Sterilization and -------*(b)(4)*----- of the syringe barrels used for manufacturing rFVIIIFc diluent occurs in the ---b(4)---------- is re-qualified –b(4)------- including the validation of specific cycles. The -------*(b)(4)*----- process of the syringe barrels is validated to guarantee a –b(4)---------- results of the recent re-qualification are provided as in the table below:

[b(4)]

-------*(b)(4)*----- of the plungers for the diluent occurs in the plunger washing machines (--b(4)----------). The plunger washing machines are re-qualified –b(4)------. The -------*(b)(4)*----- process of the plungers is validated to guarantee a –b(4)---------- for rubber closure parts. The –b(4)---------- results of the recent re-qualification of the-b(4)- plunger machines are provided in the tables below:

[b(4)]

[b(4)]

Reviewer's Comments: The firm provided the requested information. The requalification reports showed all acceptance criteria were met. The response is acceptable.

b. Please provide a description of all of the ----------b(4)--- that will be used for the vials, syringe barrel and plunger.

Biogen's response

rFVIIIFc Drug Product-Vial

-----b(4)---------- ----------

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rFVIIIFc Diluent-Syringe Barrel and Plunger

----b(4)--- ----------

---b(4)-- ----------

--b(4)-- ----------

The requalification reports for these pieces of equipment are also provided

Reviewer's Comments: The firm provided the requested information. The requalification reports showed all acceptance criteria were met. The response is acceptable.

Question 2
Regarding sterilization:

- *Please provide a description of all autoclaves used for sterilization of product contact equipment and/or components. Please provide the sterilization validation studies.*

Biogen's response
rFVIII Drug Product-Vial

--b(4)-- ----------

The autoclaves are designed for use in pharmaceutical production and for the sterilization of components and parts used in clean room –b(4)-- and the associated compounding and material preparation area.

The autoclaves have been subjected to qualification including the validation of specific cycles, all following defined protocols. The qualification cycles included both –b(4)----------
---------- studies. All process cycles are based on the parameters successfully validated in the qualification programs. The production autoclave is re-qualified –b(4)----------

The production cycles are monitored with –b(4)---------- The validated goods and positioning of the sterilization goods in the autoclave are defined in the validated loading patterns. Acceptance and rejection specifications are also documented on the loading patterns.

Defined autoclave loading patterns are used for production cycles to ensure that only validated materials are loaded and do not exceed the maximum loading established during qualification. The –b(4)- autoclaves are identical and they share a common loading pattern.

----b(4)-- ----------

----------:

1 Page determined to be not releasable: b(4)

The validation was successfully carried out.

rFVIIIFc Diluent Syringe

--b(4)---------- ----------

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The autoclave is designed for use in pharmaceutical production and for the sterilization of components and parts used in clean room –b(4)-- and the associated compounding and material preparation area.

The autoclave has been subjected to qualification including the validation of specific cycles, all following defined protocols. The qualification cycles included both –b(4)---------- ---------- studies. All process cycles are based on the parameters successfully validated in the qualification programs. The autoclave is re-qualified –b(4)------.

The production cycles are monitored with –b(4)---------- The number and location of the –b(4)-, the validated goods and positioning of the sterilization goods in the autoclave are defined in the validated loading patterns. Acceptance and rejection specifications are also documented on the loading patterns.

For requalification of loading patterns-b(4)------ load is used. The sterilization process is validated to guarantee a –b(4)----------
The results of the recent re-qualification are provided (Document number 5021235).

[b(4)]

[b(4)]

[b(4)]

Defined autoclave loading patterns, described in more details in the following section, are used for production cycles to ensure that only validated materials are loaded and do not exceed the maximum loading established during qualification. Load patterns are described in operating procedures and include criteria such as the type of materials validated, the orientation of the materials on the carts, and the placement and amount of the carts within the autoclave.

Reviewer's Comments*: *The validation reports shows the acceptance criteria were met for sterilizing vials, syringes and other product contact equipment. Defined load and fixed sterilization cycles are used. The response is acceptable.

- *Please provide a description of the autoclave used to sterilize the diluent. Please provide the –b(4)---- sterilization validation studies for the diluent.*

Biogen's response

The autoclave -----b(4)---------- is used for the –b(4)-- sterilization of the Diluent pre-filled syringe and is designed for use in pharmaceutical production.

The autoclave has been subjected to qualification including the validation of specific cycles, all following defined protocols. The qualification cycles included –b(4)---------- studies. All process cycles are based on the parameters successfully validated in the qualification programs. The requalification of the –b(4)-- sterilization is carried out –b(4)---------

The production cycles are monitored with –b(4)---------- The number and location of the –b(4)-, the validated goods and positioning of the sterilization goods in the autoclave are defined in the validated loading patterns. Acceptance and rejection specifications are also documented on the loading patterns.

For requalification of loading patterns, a –b(4)---------- load is used. The sterilization process is validated to guarantee a ------b(4)----------

Defined autoclave loading patterns are used for production cycles to ensure that only validated materials are loaded and do not exceed the maximum loading established during qualification. Load patterns are described in operating procedures and include criteria such as the type of materials validated, the orientation of the materials on the carts, and the placement and amount of the carts within the autoclave.

The initial validation of –b(4)-- sterilization cycle was performed according to defined validation plans by ----b(4)--- ----------. The results of the initial validation of –b(4)-- sterilization are described in section 3.2.P.3.5.3 of the DMF # -b(4)-. For further details please see summary reports of the initial –b(4)-- sterilization (Document no. 2771007 physical-technical part and Document no. 2771007 microbiological part). –b(4)--- ----------

The validated programs which can currently be used for –b(4)---- sterilization by using --b(4)---------- are illustrated in Table 10.

1 Page determined to be not releasable: b(4)

[**b(4)**]

Reviewer's Comments: Worst case situations have been defined with ---b(4)----------. The load is defined and a re-qualification program is in place. The response is acceptable.

Question 3

Regarding Lyophilization:

- *Please provide the study report(s) for validation of the lyophilization process and a description of the lyophilizer(s).*

Biogen's response

The lyophilizer validated for rFVIIIFc lyophilized drug product is in clean room –b(4)- at --b(4)---------- facility. The lyophilizer is manufactured by –b(4)----------. This unit

---b(4)----------
---------- ----------

In accordance with agreement reached during the CBER teleconference on 8-Oct-2013, Biogen has committed to requalifying this lyophilizer with –b(4)-- ----------. Biogen submitted a validation protocol in Amendment incorporate the feedback received from CBER on 1-Nov-2013 in the protocol.

Reviewer's Comments: The firm conducted re-validation of the lyophilizer that included empty chamber study and b(4) technical runs --b(4)----------. Please see review of the Amendment 37 and 38 for lyophilizer validation studies.

- *Please explain your approach to validating the lyophilization cycle. Required information will include the results of empty chamber temperature mapping studies for each lyophilizer you intend to employ to manufacture drug product. Please provide a summary of those studies. Please also ensure you describe your sampling method (e.g., ---b(4)----------, sampling pattern, which shelves sampled and sample locations, number of samples taken at each location), lot size of each run, fill volume of each run, product strength of each run, and testing results (e.g., ---b(4)----------).*

Biogen's response
In accordance with agreement reached during the CBER teleconference on 8-Oct-2013 for rFIXFc BLA 125444, Biogen has committed to requalifying the lyophilizer Biogen intends to employ in manufacturing rFVIIIFc drug product. As part of this requalification,
-------b(4)----------
----------. Biogen incorporated the feedback received from CBER on 1-Nov-2013 in the protocol.

Biogen also committed to –b(4)--- technical runs ----------
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vials. The draft protocols (--b(4)-- ----------) for these technical runs are attached. Biogen Idec committed to completing these technical runs around mid-November, 2013. Biogen requested feedbacks from the Agency for the protocols before conducting the study.

Additionally, Biogen also provided rationales for development of the –b(4)--- lyophilization cycle.

The rFVIIIFc lyophilization cycle consists of the following steps: --b(4)----------
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--b(4)-- ----------

--b(4)----- ----------

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--b(4)--- ----------

--b(4)---- ----------

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--b(4)-- ----------

Reviewer comments: Biogen submitted validation protocols for both the empty chamber study and technical runs, with –b(4)--- sampling plan and test plan for the technical run. Biogen also explained the rationales for the –b(4)- process cycle determination. The lyophilization cycle is based on ----------b(4)---------- ---------- data support this lyophilization cycle. I have reviewed the protocols Biogen submitted in Amendment 23 and informed Biogen that the protocols were acceptable.

- *Please clarify if validation studies were performed using vials from each qualified vendor. If not, please justify why this is acceptable.*

Biogen's response
-----b(4)-- ----------
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[b(4)]

--b(4)--- ----------

----b(4)-- ----------
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1 Page determined to be not releasable: b(4)

-----b(4)--- ----------

--b(4)-- ----------

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--b(4)--- ----------

--***b(4)***-- ----------

--***b(4)***-- ----------

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- *Please confirm that the lyophilization cycle is –b(4)-. Please provide detailed information on any changes made for any of the validation runs.*

Biogen's response

----b(4)---- ----------

[b(4)]

--b(4)----------

- *Please provide your validation final report for the corresponding validation runs.*

Biogen's response
Biogen provided their validation runs report for the following dosage strengths:

- ----b(4)- ----------
- --b(4)--- ----------
- ---b(4)-- ----------

----------**b(4)**----------

Reviewer comment: These are reports for Biogen's retrospective validation runs, and Bioegen was asked to conduct prospective validations. The prospective validation data are submitted in Amendment 37.

- *Please clarify if a study was performed for each dosage strength and fill volume. If not, please provide a justification for why this is acceptable.*

Biogen's response

---b(4)--- ----------

--b(4)-- ----------

Reviewer comment: The seven dosage strength all have the same fill volume, and considering the relatively low rFVIIIFc content ratio in the final formulation for all strength to other excipients, the difference in them are not significant for the manufacturing process. Also, the eutectic temperature measured for all dosage strengths are very similar (Refer to review of Amendment 31). I consider this bracketed approach is acceptable.

- *Please provide the final fill volumes and vial sizes for all dosage strengths.*

Biogen's response

Please find the final target fill volumes and vial sizes for all dosage strengths in Table 18.

[**b(4)**]

Reviewer comment: All dosage forms use the same fill volume, and the response is acceptable.

1 Page determined to be not releasable: b(4)

-----b(4)---- ----------

[b(4)]

----b(4)-- ----------

- *Please explain how the filled product is physically transported to the lyophilizer and how you prevent contamination of the product during this process.*

Biogen's response:
Vial filling, stopper placement, lyophilization as well as stopper closing takes place in a Grade -----b(4)---) area within a Grade b(4) environment. The crimping process takes place in a Grade b(4) area with Grade b(4) air supply.

-----b(4)-- ----------

--b(4)-- ----------

Reviewer's comment: The response is acceptable.

Question 4.
Please clarify if there are any differences in the lyophilization cycle and product testing among drug product lots: ---------b(4)-- ----------.

Biogen's response

There are no differences in the lyophilization cycle, in-process controls, or in-process testing for all the referenced drug product lots.

Release tests established at the time of process validation or conformance lot manufacture were completed for each lot.

The approaches of the heightened characterization with regard to process validation and conformance DP lots runs were the same; however, testing of the lots varied due to pre-defined requirements in protocols and/or assay limitations, e.g. –b(4)-- ----------

Reviewer comments: These drug product lots were manufactured using the same –b(4)-lyophilization cycle. No change has been made to the cycle for the additional conformance lots for the prospective validation runs as well.

Question 5.
Regarding the –b(4)---- for container closure integrity testing (CCIT):

- *Please provide the validation report for CCIT of the drug product and diluent.*

Biogen's response

Drug Product
--b(4)-- ----------

-b(4)-----
--b(4)-- ----------

---------- --b(4)----------

---b(4)-- ----------

- *--b(4)-* ----------

Biogen's response:

---b(4)-- ----------

--b(4)-- ----------

--b(4)-- ----------

--b(4)-- ----------

- *Please clarify if CCIT was done on vials from –b(4)- vendors for the drug product.*

Biogen's response:

Vials from –b(4)- vendors have been tested for container closure integrity. Report TR-PPD-003357 details the CCIT test for 3 lots of vials produced by –b(4)----------. Report TR-PPD-003676 describes the initial CCIT test for vials produced by –b(4)---. Furthermore, lot –b(4)----- was produced using ---b(4)----- vials, and CCI testing was conducted on that lot.

Reviewer's comment: The response is acceptable.

- *Please clarify if any part of the container closure system that is product contact contains latex.*

Biogen's response

No product contact components of the container closure system contains latex. The vial stopper is made of a –b(4)---------- and does not contain dry natural rubber, which is the source of latex. The formulation characteristics document (--b(4)----------) from the manufacturer is attached for reference.

The diluent syringe plunger and tip cap are made of a latex-free –b(4)----------. The manufacturer's compound data sheet (---------(b)(4)----------) was provided.

Reviewer's comment: The response is acceptable.

- *For CCIT for stability testing, please provide the –b(4)----------.*

Biogen's response:

The description of the container closure integrity testing method which includes the ---b(4)---------- used for stability testing of the drug product is given in Table 36 with acceptance criteria listed in Table 37.

[b(4)]

[***b(4)***]

Reviewer's Comment: The response is acceptable.

- *Please clarify why you used different test methods for CCIT for stability testing versus initial release.*

Biogen's response:

--b(4)-- ----------

--b(4)--- ----------

Reviewer's Comment: Biogen will use the –b(4)----- method for all release and stability testing which is more sensitive. The response is acceptable.

--***b(4)***----.
--*b(4)*- ----------

--b(4)----------

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- -----b(4)--- ----------

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- --b(4)-- ----------

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Reviewer's Comment: ***----------(b)(4)----------
----------. The response is acceptable.***

Question 7.
Regarding visual inspection:
- *Please clarify if the inspection is manual, semi-automated, or automated.*

Biogen's response
The 100% visual inspections of the rFVIIIFc drug product and diluent pre-filled syringes are performed manually.

Reviewer's comment: The response is acceptable.

- *Please describe the visual inspection procedure performed for the drug product and diluent. Information provided should include, but not be limited to, defects evaluated, acceptance criteria, and criteria for accepting or rejecting a lot.*

Biogen's response
---b(4)-- ----------

--b(4)-- ----------

--b(4)-- ----------

--b(4)-- ----------

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--b(4)----------

During visual inspection of rFVIIIFc drug product, each packaging material component is evaluated for defects such as cracks, damages, inclusions, general deviations or particulate contaminations. The lyophilized product is evaluated for defects such as particulates, glass splinters and fibers, filling volume, discoloration and the quality of the lyophilized cake itself.

During visual inspection of rFVIIIFc diluent, each packaging material component is evaluated for defects such as cracks, damages, inclusions, general deviations or particulate contaminations. The liquid diluent itself is evaluated for defects such as particulates, glass splinters and fibers, filling volume, color, and turbidity.

Acceptance criteria for visual inspection and the criteria for accepting or rejecting a lot:

Defects are classified as minor, major or critical. Table 38 indicates the criteria in place at -b(4)--------- for evaluation of the reject rate of the 100% visual inspection in relation to classification categories of minor, major or critical. The –b(4)--- procedure allows for up to -b(4)-------- visual inspections if the first inspection is above the acceptance criteria. In practice, a deviation (investigation) is initiated in the event of a failure of the first visual inspection. Thereafter, Biogen Idec ----b(4)--- jointly investigate and determine further measures (including –b(4)---------- visual inspection if required) and determination of acceptability of the lot in question.

[**b(4)**]

----b(4)-- ----------

-----b(4)----------

--b(4)----------
-----b(4)----------
--b(4)---

---b(4)-- ----------
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Reviewer's comment: The response is acceptable.

- *Please provide the qualification of your visual inspection process.*

Biogen's response

--b(4)-- ----------

----b(4)--- ----------

***Reviewer's Comment: The response is acceptable. ---b(5)----------
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Question 8.
You state, "equivalent equipment may be used," for the manufacturing of the drug product and diluent (module 3.2.A.1). Please clarify which equivalent equipment will be used and if those pieces of equipment are also validated for manufacturing rAHFFc.

Biogen's response

Currently there is no need to use equivalent equipment for rFVIIIFc drug product or diluent. In the event of a breakdown/loss of one of the listed equipment, equivalent equipment may be qualified and implemented via change control and appropriately reported to the Agency.

Reviewer's comments: The response is acceptable.

Question 9.
Regarding hold time validation for drug product, ---b(4)---------- were studied (module 2.3.P. Table 23) and product –b(4)---------- than the claimed maximum. Please adjust maximum hold times to reflect conformance lot manufacturing experience.

Biogen's Response:

Biogen understands the Agency's concern on hold time unchallenged at scale. As a result, Biogen Idec will base our specified hold times on drug product lots manufactured using the commercial process. Biogen will report and update the hold times after completion of the planned drug product process validation for the –b(4)----------.

Reviewer's comment: The firm provided revised hold time specifications during the late cycle response in Amendment 40. Please refer to review of Amendment 40.

Question 10.
Please provide your drug substance and drug product process validation protocols.
Biogen's response

DrugSubstance

The process consistency validation protocols and reports for the rFVIIIFc drug substance are provided and referenced in Table 39.

[**b(4)**]

DrugProduct

The final process consistency validation protocols and reports for rFVIIIFc drug product are provided and referenced in Table 40. As discussed during the teleconference with CBER on 23- Oct-2013, Biogen Idec is committed to prospectively validating the intermediate drug product strengths –b(4)---------- IU/vial).

Table 40: Drug Product Process Consistency Validation Protocols and Reports

Description	Process Validation Protocol	Process Validation Report
b(4) IU/vial produced under prospective validation	PVR-99-11-67	PVR-99-11-67
b(4) IU/vial produced under prospective validation	PVR-99-11-68	PVR-99-11-68
250, 500, 750, 1000, 1500, 2000 and 3000 IU/vial strengths retrospectively assessed as conformance lots	Not Applicable	PVR-99-12-48

--b(4)----------:
--b(4)-- ----------

Reviewer's comments: In the original BLA submission, Biogen submitted process validation studies for various dosages analyzed under a retrospective validation protocol. These data were deemed unacceptable, and Biogen was required to conduct the study again following a prospective validation protocol during the mid-cycle meeting. Biogen agreed to conduct lyophilizer qualification and lyophilization process validation again utilizing a ---b(4)-- ------
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Biogen submitted new lyophilizer validation protocols in this amendment. The protocol covered all key controlled parameters and acceptance criteria, in-process specifications, and sampling plan. The protocols are acceptable.

Review of Amendment STN 125487/0/26 (Nov. 12, 2013)

A teleconference was held on November 7, 2013 to discuss lyophilization validation. In this amendment, Biogen provided additional information regarding rFVIIIFc lyophilization requested during the telecon with the following information:

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--b(4)----------
---b(4)-- ----------

----b(4)-- ----------

Table 1: Composition of the Lyophilized rFVIIIFc Drug Product

Component	Quality Standard	Concentration (Pre-Lyophilization)	Quantity (per vial)
rFVIIIFc	(b) (4)	(b) (4)	
L-Histidine[2]			
Sodium chloride			
Calcium chloride, (b) (4)			
Sucrose			
Polysorbate 20			
Water for Injections (WFI)			

(b) (4)

Table 2: Physical Characteristics of the rFVIIIFc Drug product (b) (4) Formulation

rFVIIIFc Drug Product Strength	(b) (4)
(b) (4)	

(b) (4)

3 pages determined to be not releasable: b(4)

- ---b(4)----------
- ----b(4)----------
- -----b(4)----------
- ---b(4)----------

These manufacturing runs are to be conducted to validate the ----------(b)(4)---------- rFVIIIFc lyophilized drug product manufacturing process on –b(4)---------- filling line in –b(4)----------. The primary objective is to confirm that these specified dosage strengths of rFVIIIFc lyophilized drug product manufacturing process results in a product that predictably, consistently, and uniformly meets the predefined acceptance criteria.
-----b(4)----------. The protocol specified the vials, stoppers and crimping seal/flip cap to be used, and in-process control specifications and acceptance criteria. It provided list of required reports/documentation, as well as a list of all analytical methods to be used and related SOPs. Sampling plan is also provided; positional samples were taken by ----b(4)----------

Reviewer's comment: The validation protocols cover only the DP compounding, sterilizing filtration and lyophilization steps. Biogen provided extensive sampling plan, sample testing plans, acceptance criteria, as well as deviation and investigation procedures. Related validation and reports for facilities and equipment are also provided. The protocols are acceptable.

Review of Amendment STN 125487/0/28 (November 21, 2013)

An information request was sent to Biogen on November 1, 2013 regarding the manufacturing facilities including concurrent manufacturing policy, room usage within purification suite, and EM data for all –b(4)-- purification suites. Biogen provided a summary of prevention of cross contamination in the purification suites including summary of gowning procedures, clarification on the manufacturing areas that are classified as closed system, equipment movement and traceability, environmental monitoring trend charts covering January to June 2013 for the –b(4)----- purification suites, and also in-process –b(4)---------- release testing results from b(4) batches made in Suite-b(4)-. A summary for equivalency of the –b(4)---- purification suites was provided, and no difference in EM trending was observed.

Manufacturing Area Usage in rFVIIIFc Process Validation and Commercial Manufacturing
The purification area review has been covered in review of Amendment 21 and 24, and Biogen only seeks licensing of ----b(4)---------- purification suites in Purification b(4) area.

Prevention of Cross Contamination in the Purification Area
Biogen has multi-product manufacturing procedures in place to prevent cross contamination including gowning, traffic flow, labeling, color coding, and spatial segregation of clean and soiled equipment that is identified by product.

In practice, only one product is actively processed in one purification suite during a campaign. The amendment discussed segregation policies for pre-viral and post-viral operations in the purification suites. All Class –b(4)--- process rooms in the purification b(4) have dedicated air handling system and no re-circulation of air is shared among any b(4) process rooms. The dispensing room (-b(4)----) is equipped with Class –b(4)---------- specifically for DS dispensing operation. The –b(4)----- may be used for dispensing more than one product during a campaign, but only one product is allowed in the room at a time. The –b(4)-- require enhanced procedures for room cleaning, equipment preparation and cleaning, and personnel gowning prior to use.

Biogen outlined their room and equipment change over policies. A line clearance must be performed before the processing of the next product. Each product being manufactured has a unique color identifier. Equipment is affixed with a colored medallion designating the product being manufactured. Color coded medallions are used as a source of segregation for small equipment. Rooms also have signage depicting the color and product. These identifiers are updated as part of the changeover process and are reviewed and approval by quality before commencement of a new campaign. Gowning and personal sanitization procedures are in place to prevent cross contamination that included specific procedures for entering and re-entering specific process rooms. More stringent procedures are in place for dispensing room in terms of gowning and flows.

EM data including trend charts for various EM parameters (particle counts, surface, viable air, etc.) from first half of 2013 for Purification b(4) Area is provided, and results demonstrate effective, consistent and comparable environmental control of all purification suites.

Reviewer's comment: Biogen provided additional information for the manufacturing areas in support their request for licensing of the –b(4)- purification suites in Purification b(4) area. The information regarding cross contamination prevention policies and historic EM data provide sufficient assurance of the equivalency and control of the –b(4)- suites.The response is acceptable.

Review of Amendment STN 125487/0/30 (Nov. 27, 2013)

Mid cycle CMC response, product office related IR questions 11 to 30

Question 18.
Please revise acceptance criteria for the following release tests, as indicated:

- *Please establish an acceptance criterion for endotoxin that reflects manufacturing capability and is consistent with the drug product release specification. The proposed acceptance criterion of –b(4)--- neither reflects conformance batch results, ----b(4)---------- ---------- nor is consistent with the highest proposed drug product release specification of –b(4)--------*

Biogen's response

The specification limits that are currently proposed are based on the established safety limits as presented in the current –b(4)-------. Data collected to date is a reflection of the current

manufacturing process and all data are within the method limit of quantitation –b(4)---------- for drug substance.

An action limit will be established at ----------b(4)---------- All results that exceed this limit will be investigated before the batch disposition is determined. Drug product action limits will be similarly set at –b(4)---------- to provide for a consistent limit across all strengths and is reflective of the manufacturing process.

The DP endotoxin specifications were proposed independently based on compendial safety limits for endotoxin. Given the typically –b(4)---------- during DP manufacturing –b(4)----------) the proposed ----------b(4)---------- is consistent with the proposed limits for DP.

Reviewer's comment: The response is not acceptable. The proposed set in-process specifications (IPS) for –b(4)---------- with the justification that the –b(4)------process for drug product manufacture will ----b(4)---------- to drug product release specifications does not provide a high degree of confidence in continued attention to manufacturing control in light of manufacturing experience that indicates Biogen's ability to control ---b(4)---------- levels consistently to –b(4)----------. During the late cycle meeting, Biogen agreed to tighten this IPS, and refer to LCM response Amendment 40 for review of the revised IPS proposal.

Question 19.
Please establish in-process specifications (IPS) for ---b(4)---------- that reflect manufacturing capability.

Biogen's response

Biogen Idec agrees to establish in-process –b(4)---------- control limits consistent with manufacturing capability.

--b(4)---------- ----------

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1. ***Alert level****:* This level was established as a preliminary internal notification level. Exceeding this limit results in departmental notification and requires an investigation within Biogen Idec's deviation system. This level was established to ensure that the responsible department reviews the results for trends and takes action if data supports a trend is evident.

2. ***Action limit****:* This level was established based upon normal operational ranges and capabilities. Exceeding this limit results in departmental notification and a deviation is issued against the affected batch. This level was established to ensure that the responsible department conducts an investigation into the possible cause for the microbial excursion and takes appropriate action to minimize future excursions.

3. ***Specification limit****:* This limit is established as a potential batch rejection limit. Exceeding this limit results in departmental notification, issuance of an Out of Specification (OOS), and batch rejection if the OOS is confirmed.

----b(4)-- ----------

Limited data was available from the rFVIIIFc manufacturing process at the time of BLA filing. As more manufacturing data is available now, microbial control limits specified for rFVIIIFc have been reviewed and compared to historical manufacturing data. The Company agrees to –b(4)-- the in-process limits as shown in Table 3 for –b(4)------ and Table 4 for -b(4)-----. The prescribed –b(4)------ levels for in-process –b(4)---------- have been modified as follows, based on historical manufacturing data:

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- --b(4)-- ----------

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---b(4)-- ----------

---b(4)----------
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- -----b(4)---------- ----------

--b(4)-- ----------

--b(4)-- ----------
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1. ---b(4)-- ----------

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2. –b(4)--- ----------

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3. –b(4)-- ----------

--b(4)----------
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[**b(4)**]

[b(4)]

----***b(4)***-- ----------

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etc., and does not include sterile injectable products. During LCM, Biogen agreed to provide tighter IPS and refer to LCM response in Amendment 40 for review of the new proposed IPS.

Review of Amendment STN 125487/0/31 (Dec. 3, 2013)

A teleconference was held on November 21, 2013 regarding lyophilization validation, and Biogen submitted this amendment to provide information on –b(4)---------- of rFVIIIFc DP and –b(4)---------- analysis report.

------b(4)----------
----b(4)-- ----------

[b(4)]

[b(4)]

--b(4)----------
---b(4)-- ----------

[b(4)]

---***b(4)***-- ----------

Review of Amendment STN 125487/0/36 (Feb. 11, 2014)

During a combined teleconference with BLA STN125444/0 and BLA STN125487/0 on Oct. 8, 2013, Biogen agreed to re-conduct Lyophilizer validation for rFVIIIFc. In this amendment, Biogen submitted completed product temperature mapping and extensive sampling for quality testing (referred to as technical runs) within the lyophilizer for rFVIIIFc drug product at –b(4)- as follows:

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- --b(4)-- ----------

- --b(4)-- ----------

- ---b(4)-- ----------

--**b(4)**----------
--b(4)-- ----------

--b(4)------
--b(4)---- ----------

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5 Pages determined to be not releasable: b(4)

[b(4)]

--b(4)-- ----------

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--b(4)----------

Review of Amendment STN 125487/0/37 (Feb. 28, 2014)

Biogen completed the prospective validations of ----b(4)----------/vial strengths in support of rFVIIIFc lyophilization process as agreed upon during the Oct. 8, 2013 telecon using validation protocol submitted on November 15, 2013 in Amendment 27. This amendment contains a summary of the data available from the three drug product process validation studies at –b(4)---------- facility and from characterization studies of the DS batches used including:

1. ----------b(4)-- ----------

---b(4)-- ----------
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2. ---b(4)-- ----------
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3. –b(4)----------
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4. –b(4)-- ----------

Data for critical controlled parameters, in-process tests, in-process controls, a uniformity analysis, and conformance to the certificate of analysis/conformance are included. Each of the three validations runs conformed to the pre-defined acceptance criteria and all deviations were assessed and found not to impact the validity of the study.

--b(4)-- ----------

--b(4)---------- ----------
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[b(4)]

2 Pages determined to be not releasable: b(4)

[b(4)]

--b(4)----------

Review of Amendment STN 125487/0/40 (April. 9, 2014)

A late cycle meeting (LCM) was held with the Biogen on March 20, 2014. There were seven CMC/Product substantive review items were conveyed to Biogen before the meeting and discussed during the meeting. This amendment contains responses for items #1 through #7.

Review item # 1

Your Response in amendment 30 to item 18b from the September 11, 2013 information request was inadequate. Please revise the drug substance release specification for ---b(4)----------

Biogen's Response

---b(4)--- ----------.

--b(4)--- ----------

Review item # 2

Your Response in amendment 30 to item 19 from the September 11, 2013 information request was inadequate. Please align in-process specification (IPS) for ----(b)(4)------- with those listed in CMC-1 (Table 1).

[**b(4)**]

--b(4)----------
--b(4)-- ----------

[**b(4)**]

----*b(4)--* ----------

Review item # 3
Process validation reports submitted to amendment 37 indicated that established process hold times far exceeded manufacturing experience for the validated process. Please align process hold time limits during drug product manufacture with conformance lot manufacturing experience.

--b(4)----------
---b(4)-- ----------

[b(4)]

Reviewer's comment: Biogen proposed revised hold times for the DP manufacturing process based on manufacturing experience with the validated process. Biogen's request that the Agency consider a –b(4)-. maximum process time for the filling operation based on support from media fill studies is acceptable. The response is acceptable.

Review item # 4
TRN205654 for an out of specification (OOS) result for Factor VIII potency, associated with process validation report, TR-PPD-006668 revealed the practice of averaging an OOS result with a result meeting specification generate a reportable result within specification. Please be advised that this practice is unacceptable under any circumstances.

Biogen's response
Per Biogen Idec's practices, it is never acceptable to average out of specification (OOS) results with a passing result(s) for release, stability or in-process samples to obtain a passing result. Biogen Idec operates in alignment with cGMPs and all applicable regulatory guidelines including the FDA Guidance for Industry "Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production."

Reviewer's comment: The response is acceptable.

Review item # 5
--b(4)-- ----------

Biogen's response
--b(4)-- ----------
1. –b(4)----------
2. –b(4)---- ----------
3. –b(4)-- ----------

--b(4)-- ----------

The response is acceptable.

Review item # 6
Please note that we are waiting for the re-qualification report for container closure integrity testing of the diluent syringe as committed in amendment 25.

Biogen's response
The re-qualification report for container closure integrity testing of the SWFI diluent syringe was submitted to the BLA on March 31, 2014 under Sequence # 0038.

***Reviewer's comment: See review of Amendment #38* received on March 31, 2014.**

Reviewer's item # 7
Please note the Final Rule for 21 CFR part 4-Regulations of combination Products became effective July 22, 2013. The pre-filled diluent syringe is considered a combination product [21CFR 3.2(e)]. It appears that you have chosen to demonstrate compliance with the drug cGMPs. Please ensure you have complied with the following provisions of the Quality system (QS) regulations for the pre-filled diluent syringe:
a) 21CFR § 820.20. Management Responsibility
b) 21CFR § 820.30. Design Controls
c) 21CFR § 820.50. Purchasing Controls
d) 21 CFR § 820.100. Corrective and preventative action

Biogen's response
Biogen provided an overview of the current Quality System between Biogen Idec, -b(4)-- and the diluent syringe component suppliers to achieve the controls required by 21 CFR 820 that included internal procedures for managing the suppliers, the risk, the changes, and the CAPA according to 21 CFR 820.

Reviewer's comment: The response is acceptable.

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